

The 2.0 Å Structure of Malarial Purine Phosphoribosyltransferase in Complex with a Transition-State Analogue Inhibitor

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Malaria is a leading cause of worldwide mortality from infectious disease. *Plasmodium falciparum* proliferation in human erythrocytes requires purine salvage by hypoxanthine-guanine-xanthine phosphoribosyltransferase (HGXPRTase). The enzyme is a target for the development of novel antimalarials. Design and synthesis of transition-state analogue inhibitors permitted cocrystallization with the malarial enzyme and refinement of the complex to 2.0 Å resolution. Catalytic site contacts in the malarial enzyme are similar to those of human hypoxanthine-guanine phosphoribosyltransferase (HGPRTase) despite distinct substrate specificity. The crystal structure of malarial HGXPRTase with bound inhibitor, pyrophosphate, and two Mg²⁺ ions reveals features unique to the transition-state analogue complex. Substrate-assisted catalysis occurs by ribooxocarbenium stabilization from the O5' lone pair and a pyrophosphate oxygen. A dissociative reaction coordinate path is implicated in which the primary reaction coordinate motion is the ribosyl C1' in motion between relatively immobile purine base and (Mg)₂-pyrophosphate. Several short hydrogen bonds form in the complex of the enzyme and inhibitor. The proton NMR spectrum of the transition-state analogue complex of malarial HGXPRTase contains two downfield signals at 14.3 and 15.3 ppm. Despite the structural similarity to the human enzyme, the NMR spectra of the complexes reveal differences in hydrogen bonding between the transition-state analogue complexes of the human and malarial HG(X)PRTases. The X-ray crystal structures and NMR spectra reveal chemical and structural features that suggest a strategy for the design of malaria-specific transition-state inhibitors.